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Extracted from the American Journal of the Medical Sciences for October, 1882.

THE DIGESTIVE POWER OF COMMERCIAL PEPSIN IN ARTIFICIAL DIGESTERS AND IN THE STOMACH.

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Pepsin in most respects resembles a true chemical ferment, *i. e.*, it acts in minute quantity without great loss to itself. It will only digest in acidulated solutions, the amount of acidity varying between .1 per cent. and 1 per cent. of free HCl (see later on). Pepsin acts almost exclusively upon albuminous matters. Its action in a given solution ceases after a certain time. Addition of acid or withdrawal of digested products prolongs the action, but it will eventually stop not to be renewed, the ferment being either decomposed or used up.

Pepsin exists in the gastric juice in extremely minute proportion. The exact per cent. is not known. The pure ferment has never been obtained in sufficient amount for accurate analysis. It seems to have something of the composition but none of the reactions of a proteid. Prepared pepsins are mixed normally with peptone and other albuminous matters; commercial pepsins are generally mixed with starch, sugar, etc.

Investigations into the value of pepsins artificially obtained have been made by Sieveking,[1] in 1857, by Pavy,[2] in 1863, Guibourt,[3] in 1865, Tuson,[4] in 1870. Since then by a great many persons, *e. g.*, A. Petit,[4] Dowdeswell,[5] Golowatschon,[6] Ewald,[7] Lees,[8] Sée,[9] and Langley.[10] In this

[1] Med. Times and Gazette, 1857.
[2] Journal de Pharm. et de Chem., 1865.
[3] Lancet, Aug. 1870.
[4] Same, Jan. 1880.
[5] Practitioner, 1880.
[6] Zur Lehre über den Process des Magens. Inaug. Dissert., Moskau, 1880.
[7] Lectures on Digestion, Berlin, 1878–9.
[8] Brit. Medical Journal, March and April, 1880.
[9] Journal de Thér., viii. 4, p. 125, 1880. See also F. Kessler, Inaug. Dissert., Dorpat, 1880, and Schmidt's Jahrbuch., clxix. p. 234.
[10] Journal of Physiology, Jan. 1882.

country Mr. E. Sheffer first studied it systematically.[1] He was followed by J. S. Hawley,[2] Kretzschmar,[3] Wreen, Squibb,[3] Lankford and others.

It would seem that the working power of pepsin ought to be very exactly known. This is not the case, however, practically, and it must be remembered that many of the above experimenters only attempted to cover special grounds. The standard adopted by the British Pharmacopœia is: one grain of pepsin should dissolve one hundred grains of coagulated egg-albumen in six hours at a temperature of 100° F.

According to a report made to the American Pharmaceutical Association,[4] from five to ten parts of pepsin should dissolve at least one hundred and twenty parts of egg-albumen at a temperature of 104° in five or six hours. Petit, Dowdeswell, and most of the German experimenters found that the majority of pepsins came up nearly to the British standard.[5]

My own and other experiments show, however, (1) that different brands have different strength; (2) that the same brand may vary in strength at different times; (3) and that there are a number of details connected with the process of artificial digestion by which the power of the pepsin can be greatly modified. Thus a pepsin can be made to do four times its usual work by keeping the temperature at 50° C. (Petit); much more work can be done by increasing the amount of pepsin, by finely mincing and constantly stirring the albumen, by digesting in a large broad vessel, accessible to air, by occasionally adding acid, and by removing digested products. We have no official standard test covering all these points, although such a thing is much needed.

As a rule, the declarations upon labels regarding the power of the pepsin are utterly unreliable. The results claimed will not be obtained unless special precautions be taken and not always then.

I made a series of experiments with the following objects:—

1st. To test the comparative value of various pepsins.

2d. To test their absolute value (outside the stomach) under conditions not so artificial as those sometimes employed. I wished to find, not how much pepsin *could* do, but what it *would do under ordinary conditions.* I did not, therefore, mince the albumen in all cases, since it is in no such condition in the stomach; but cut it into thin slips or small pieces, or chewed it and then spat it into the digesting bottles. In nearly all cases I tested a number of pepsins at the same time. The solutions were put in receptacles of about the same size and shape, and were stirred at intervals of a half or one hour. The solutions were acidulated with hy-

[1] Am. Journ. of Pharmacy, Feb. 1882.

[2] Proc. of Med. Soc. of Co. of Kings, Aug. 1878. [3] Ibid., May, 1880.

[4] A Medical Formulary, by L. Johnson, M.D., 1881, p. 290.

[5] In the practical manufacture of peptones Chapoteaut finds that one part of pepsin digests fifty parts of raw, lean, minced beef *in fourteen hours at a temperature of* 113° *to* 123° F.

drochloric acid to the extent generally of .5 per cent. of the concentrated acid.[1] Sometimes the amount was increased to 1 per cent. The latter is more favourable to artificial digestion, but the former is nearer the normal acidity of the gastric juice. Different amounts of pepsin, of acidulated water and of albumen were employed. To determine the actual work of the pepsin I took out all the undigested matter at the end of a certain number of hours and dried it. It was then partially dried, weighed, and compared with the original amount. Such a method does perfectly well for comparative experiments and to test the practical working of the ferment. It assumes that all the dissolved matter is digested. This I believe to be essentially the case, for reasons which will be shown further on. I do not mean to assert, however, that the dissolved matter is all peptone.

I used in all cases as a test the ordinary digestive one. The test of pepsin by its power to coagulate milk is of no value. Similarly the chloride of sodium test is, I believe, not a reliable one.[2]

EXPERIMENTS.

SERIES I. No. 1.—Took water acidulated with HCl .5 per cent., ℥ss.
Pepsin (American), gr. v.
Coagulated albumen, cut into small strips, gr. xx.
Kept at temp. 80° to 100° F. for 12 hours.

Result.—Slight disintegration with gelatinous appearance on the edges of the strips.

No. 2.—Same result.

No. 3.—Substituted raw beef for albumen. About same result.

No. 4.—Substituted cooked chicken, white meat, for albumen. Same result.

The water was not sufficient, nor the temperature high enough to make these results of value alone.

No. 6.—℞. Lean beef cut into fine strips, ℥ss.
Pepsin (Keesby and Mattison's), gr. x.
Acidulated with HCl .5 per cent., ℥iv.
M. Kept at temp. 100° F. for 4 hours.

No. 7.—Same.

No. 8.—Same, but substituted Fairchild's pepsin (old preparation).

Result.—The strips of meat swelled up, became somewhat gelatinous, but no absolute disintegration.

SERIES II.—Took pepsin of various kinds, gr. x.
Water acidulated with HCl, conc. .5 per cent., ℥ij.
Albumen coagulated, cut into long and narrow strips, gr. xxx.
Put at temp. 100° F., shaken every hour, kept in 8–9 hours.

[1] There would be a slightly less amount of the free acid.

[2] See discussion on this subject, Proc. of Medical Soc. of Co. of Kings, Aug. 1878.

Results.—At the end of 4 hours considerable changes; swelling, softening, some disintegration.

At end of 8 hours there was left of dried albumen (which contains about one-half as much water as coagulated albumen) the following amounts:—

		Dried Albumen.
(*a*)	In solution containing Hawley's pepsin,	gr. j.
(*b*)	" " " Merck's (not pure) pepsin,	gr. j.
(*c*)	" " " Boudauldt's " "	gr. ij.
(*d*)	" " " Merck's (pure) "	gr. v.
(*e*)	" " " Fairchild's, in scales (old preparation) pepsin,	gr. j.
(*f*)	" " " Wyeth's pure pepsin,	gr. vij.
(*g*)	" " " Lacto-peptin,	gr. xv.

Special Preparations.

(*h*) ℞. Fairchild's essence of pepsin, ℥ij.
Aquæ, ad ℥ss.
Albumen coagulated, gr. x.
M. At temp. 100° F. 8 hours.
Result.—A slight amount of softening only.

(*i*) ℞. Caswell & Hazard's lime juice and pepsin, ℥ij.
Aquæ, ad ℥vj.
Coagulated albumen, gr. x.
M. At temp. 100° F. 8 hours.
Result.—None apparent.

(*k*) ℞. Lacto-peptin, gr. x.
Albumen, gr. xl.
Aquæ acidulated with HCl .5 per cent. ℥vj.
M. Temp. 100° F., 8 hours.
Result.—Slight diminution in bulk apparent.

(*l*) ℞. Fairchild's pepsin (old preparation) in scales, gr. iij.
Albumen, finely cut, gr. x.
Aquæ acidulated with HCl .5 per cent., ℥vj.
M. Kept at temp. 100° F. 8½ hours.
Result.—Albumen all dissolved.

(*m*) ℞. Wyeth's purified pepsin, gr. j.
Albumen, gr. x.
Aquæ acidulated with HCl .5 per cent., ℥j.
M. Temp. 100° F. 4 hours.
Result.—Dried albumen, gr. ij.

The above experiments gave less than standard results. This was partly due to the albumen being cut up, not mashed or minced finely, and not stirred frequently.

They show (1) that only slight results can be gotten from pepsins unless every precaution is carried out. (2) That the different pepsins have different values. (3) That lacto-peptin and the so-called essences and elixirs of pepsin are feeble preparations.

SERIES III. No. 1.—Took coagulated finely cut albumen, gr. xxx.
Aquæ acidulated with HCl .5 per cent., ℥vj.
Pepsin (Hawley's), gr. xx.
M. At temp. 100° F. 6 hours.

No. 2.—The same, with gr. iij Boudauldt's pepsin, instead of gr. xxx of Hawley's.

Results.—In (1) gr. vj dried albumen.
" (2) gr. xv " "

The above experiments were to see whether an increased amount of acidulated water or pepsin would increase the effect. As far as they go they show that more water does not increase the result much, while more pepsin does. This latter agrees with the results of others. The effect of increased dose is not greater in the same ratio, however.

SUPPLEMENTARY.—At same time with above, tests were prepared in strict accordance with a label.

(*a*) ℞. Pepsin (Sheffer's), gr, x.
Albumen (coagulated and finely cut), gr. 140.
Aquæ acidulated with HCl 1. per cent., ℥j.
M. Kept at 100° F. for 6 hours.

Results.—Almost nothing; hardly any change perceptible.

(*b*) Same as (*a*), but reduced albumen to gr. xx.

Result.—In 6 hours albumen partly dried, gr. x.

(*c*) Same as (*a*), but increased acid. aq. to ℥iv.
Decreased pepsin to gr. v.

Result.—In 6 hours albumen partly dried, gr. xl.

To test effect of larger dose and more acidulated water:—

(*d*) ℞. Aquæ acidulated HCl .5 per cent., ℥iv.
Coag. albumen, gr. 120.
Pepsin (various kinds), gr. xl.
M. Kept at 100° F. 6 hours.

Result.—Albumen partly dried, gr. 80.

Sheffer's, Boudauldt's, Wyeth's, and Merck's were equally mixed.

SERIES IV.—℞. Pepsin, of various kinds, gr. x.
Aquæ acidulated with HCl .5 per cent., ℥ij.
Albumen (finely chopped), gr. 120.
M. Kept at temp. 100° F. 5 hours.

1. *Result.*—With *Sheffer's* pepsin albumen, partly dried, weighed, gr. 40.

*

2. *Result.*—With Keasby & Mattison's, gr. 60.

3. *Result.*—With Fairchild's old preparation, gr. 50.

SERIES V.—Took eight different kinds of pepsin and made a mixture as follows:—

Pepsin, gr. x.
Aquæ acidulated with HCl .5 per cent., ℥iij.
Albumen coag. (chewed and then spat out), ℥ij.
Kept at a temp. 110° F. for 6 hours, stirred q. 1 hour.

The albumen left was then put on a filter paper, dried, and weighed, with the following results:—

In mixture with Beal's pepsin, gr. viij.
" " " Boudauldt's pepsin, gr. xij.
" " " Sheffer's " gr. xxv.
" " " Merck's* " gr. xxi.
" " " Frinzuber* " gr. x.
" " " Fairchild's* (new) pepsin, gr. xxiv.
" " " Hawley's pepsin, gr. xxv.
" " " Witte's* " gr. xix.

In those marked * the dose is, gr. 1–3, and they are called "pure." The claims of all are that gr. j to gr. x will digest gr. 150 to gr. 225, or even gr. 500 of albumen in 4–6 hours.

From the above experiments it seems possible that most could do it if the albumen were minced finely, frequently stirred, and the HCl was in proportion of 1 per cent.

Supplementary trials of Fairchild's and Witte's pepsin, for which much is claimed:—

(1) ℞. Fairchild's pepsin (new), gr. x.
Acidulated water with HCl 1. per cent., ℥v.
Coagulated albumen, finely cut, gr. 240.
M. At temp. 100°–110° F. 3 hours, stirred quietly 1 hour.
Result.—About gr. 60 dried albumen left.

(2) ℞. Witte's pepsin, gr. x.
Aquæ acidulated with HCl 1 per cent., ℥iv.
Coagulated albumen (chewed), ℥ij.
Result.—In 3 hours at 100°–110° F. about gr. 60 dried albumen.

(3) Same as (1), only the albumen was chewed.
Result.—Gr. x partly dried albumen. This was the best result ever obtained.

(4) Took Fairchild's pepsin scales, gr. v.
Acid. hydrochloric. .5 per cent.
Aquæ, ℥v.
Lean mutton cut and chewed, gr. 120.
Coagulated egg albumen cut and chewed, gr. 380.

(5) Same mixture, except that Sheffer's pepsin was used.
Kept both at temp. of 102° to 110° F. for five hours, and stirred about every half hour.

Result.—In experiment (4) gr. 420 of partly dried residue; in experiment (5) gr. 480 of partly dried residue.

(6) Took Hawley's pepsin, gr. x.
HCl .5 per cent.
Aquæ, ℥v.
Broiled tenderloin, cut and finely chewed, gr. 480.
Kept 4 hours at 102° to 110° F., occasional stirring.

Result.—Weight of partly dried residue, gr. 440.

Series VI.—Test of Extract of Pancreas (Fairchild's).
Took gr. x pancreatin.
" ℥j aquæ with HCl 1. per cent.
" gr. x Fairchild's pepsin.

M. Kept at temp. 100° F. for 2 hours, then neutralized fluid with sodæ bicarb., and added ℥iij to ℥iv milk. Did this with three samples. Kept the milk and pancreatin mixture at temp. 100° F. for 7 hours. No evidence of peptonization.

A few other special experiments were made to test the action of pepsins on lean meat, and the comparative value of two preparations used in later experiments. In mixtures made according to label in four experiments, using Hawley's and Boudauldt's pepsins, lean meat, cut into strips of moderate size, was swollen and softened, but hardly at all dissolved in five hours.

The above experiments appeared to me to show that *ten grains of ordinary commercial pepsin will generally digest ten or twelve times its own weight of coagulated egg-albumen, finely minced in four to six hours. It has, however, a very little effect upon lumps of albumen or upon boluses of lean or cooked meat.*

This is the case outside the stomach. If it does no better when given medicinally, or even if it does considerably better, its power as a remedy must be very slight.

Doubts regarding the efficacy of pepsin are quite prevalent among medical practitioners.[1] But on the whole, the clinical evidence is in favour of it, as shown by the immense demand, and by the many testimonials in text-books and journals.[2] I have certainly had cases under my personal observation which showed that it had positive value. The great variation in the quality of pepsins, and the ignorance of the proper way in which to give them, will explain some of the failures in its use.

I wished, however, to discover if possible, by actual observation,

[1] See especially Wood's Mat. Medica and Therapeutics, 3d ed., Art. Pepsin.

[2] Dr. Sanford furnished some positive clinical evidence of its value in a discussion before King's Co. Med. Soc. *Vide* Proc., Aug. 1878.

whether pepsin, given medicinally, has not a much greater power than would be inferred by its action in digesters. There are physiological reasons for supposing that it has. But, after all, a physiological hypothesis is a poor substitute for a demonstration. This latter is what I have sought.

I therefore took a large number of dogs, fed them upon certain fixed quantities of food, giving pepsin with the food to some, but only the food to others. They were then killed, and the condition of the food noted.

I am aware of the opportunities for error in such experiments, and will discuss them and show that they were as nearly as possible met.

First, the experiments were on dogs, not human beings. But man is more of a carnivora than omnivora. Stomach digestion in the dog, as compared with intestinal, is of somewhat greater importance than it is in man. The ratio of the length of man's intestine to his body is about 1 to 6; of dog's 1 to 5–6; of herbivora's 1 to 12–28.[1] The ratio of the superficial area of stomach to that of intestine in man is 20 to 100; in carnivora 19–28 to 100.[2, 3] The dog's stomach is relatively a little larger than man's therefore. But the gastric glands and juice are essentially of the same character. Digestion reaches its height in about two hours[4] in the dog, it then gradually declines. Gastric digestion in the dog is on the whole a little slower than in man, and of a little more relative importance. But the difference is not great.

Second. The experiments would have value only in one direction. If no results were obtained, no positive inference either way could be laid down. Positive results, however, would have a real value, being obtained against serious obstacles.

Third. The individual results would depend upon the size, health, age, etc., of the different animals. The dogs, therefore, were carefully chosen, were of about the same size, and were deprived of food for twenty-four hours.

Fourth. The same pepsins would have to be used. This was done.

Fifth. The experiments were made on animals with healthy stomachs. But if pepsin shows an extra activity here, we can justly infer that it would do the same in dyspeptic stomachs. However, I performed some control experiments upon animals with a presumably artificial dyspepsia produced by morphine.

As food, coagulated egg-albumen and lean meat were used. After the animals were killed, the contents of the stomach were carefully collected, pressed upon filtering paper, weighed, and the weight compared with that of the original amount.

[1] J. Munk. Physiol. des Menschen und Säugethiere, p. 140. Berlin, 1881.

[2] In a dog weighing twelve pounds I found the small intestine twelve feet long, the large intestine one foot and a half. Capacity of stomach, ℥xiij.

[3] Custor, J., Marbürger. Sitz. Ber. No. 7, Oct. 1879.

[4] Schmidt-Mulheim, A. Archiv für Anat. and Phys., 1879, p. 39.

I should add that the animals were all condemned to be drowned, so that no cruelty or unnecessary loss of life was involved.

From the following table it will be seen—

(1) That in 21 dogs to whom were given ℥ 84 of albumen and lean meat, *and gr.* 240 *of pepsin*, there were digested ℥ 63 gr. 17, or about four-fifths of the whole, or on an average ℥iij gr. xij for each dog, within one and three-quarters to three and a half hours.

(2) That in 10 dogs of Series I. V. VI., to whom were given ℥ 40 of albumen and meat *with gr.* 130 *of better pepsin*, there were digested ℥ 34 gr. 27, or about seven-eighths of the whole, or an average of ℥iij gr. 50 for each dog.

(3) That in 15 dogs, to whom were given ℥ 60 of meat and albumen, *with no pepsin*, there were digested ℥ 21 gr. x, or a little over one-third or about ℥j gr. vj for each dog.

This gives a difference of from 126 *to* 158 *grains in favour of the pepsin* for each trial. Furthermore, the digestion was all done *within three hours*, or three and a half in a few cases. It is to be remembered, also, that the albumen was not cut up, and was only coarsely broken by the dog's teeth. The meat was in a solid mass.

Now *it is impossible* for any commercial pepsins in ten or fifteen grain doses to digest the above amount of *unminced* albumen, outside the stomach, except possibly after twenty or thirty hours. Even if minced, it could not do it within three hours.

The above dose of pepsin *will make hardly any impression* on beef, rare or cooked, when given as above, in three or even six hours.

I think it can be fairly inferred, therefore, that I have demonstrated an extra activity of medicinal pepsins when in the stomach.

It is not easy to produce by statistics the impression made by personal observation of the stomachs. I often saw the mucous membrane, in the vicinity of the pepsined meat, of a fiery-red colour, but never saw it so marked about the non-pepsined food.

In my second and third series the pepsin action seemed to have become much less. It finally occurred to me that the pepsin, though of the same brand, might not be so active as at first, especially upon meat. I changed the pepsin and at once got such marked results that it seemed unnecessary to make further experiments. I have, therefore, for the first, fifth, and last series, made a separate estimate.

Tabular Record of Experiments to Test the Activity of Commercial Pepsins in the Stomach.

Series.	No. of dogs (full grown) with weight.	Kind and amount of food.	Time allowed for digestion.	Kind and amount of pepsin.	Contents of stomach, aside from the food and pepsin.	Weight of food at end of digestion.			
						When given *with* pepsin.	Amount digested.	When given *without* pepsin.	Amount digest'd
	No. lbs.								
I.	1 10	Coagulated egg, album. ℥ss	3 hrs.	Hawley's gr. x	Empty	gr. ij (almost gone) a few "flocculi."	gr. 238		
	2 10	"	"	"	"	.....	.....	℥iij (not much apparent change)	gr. 60
	3 15	"	"	"	"	.....	.....	℥iij "	gr. 60
	4 12	"	"	"	"	gr. iij	gr. 237		
	5 15	"	"	"	"	gr. ij	gr. 238		
	6 12	"	"	"	Hair and foreign substance	gr. xl	gr. 200		
	7 12	"	2½ hrs.	"	Some bread	.....	.....	℥i	gr. 180
II.	8 12	"	3 hrs.	"	"	.....	.....	℥iv (hardly any percept. ch.)	0
	9 12	Raw lean meat ℥ss	"	"	Empty	.....	.....	℥iv (hardly any percept. ch.)	0
	10 12	Coag. egg alb. ℥ss	"	"	"	Only traces (flocculi)	gr. 240		
	11 10	Raw lean meat ℥ss	"	"	"	"	gr. 240		
	12 8	Coag. egg alb. ℥ss	"	"	"	℥iv (hardly any change)	0		
	13 15	"	"	"	"	℥iiss	gr. 90		
	14 12	"	"	"	"	℥ij	gr. 120		
	15 15	"	"	"	"	.....	.....	℥iv "	0
III.	16 10	Raw lean meat ℥ss	2½ hrs.	"	Hairy masses	℥iij (much foreign matter)	gr. 60		
	17 12	"	"	"	"	℥ij	gr. 160		
	18 12	"	"	"	Empty	No traces; vomited?			
	19 15	"	"	"	"	.....	.....	℥ij	gr. 120
	20 12	"	"	"	"	.....	.....	℥j–gr. xij	gr. 168
	21 10	"	"	"	"	.....	.....	℥j–gr. l	gr. 130
IV.	22 16	"	3 hrs.	"	"	gr. l	gr. 190		
	23 16	"	"	"	"	.....	.....	gr l	gr. 190
	24 12	"	"	"	12 lumbricoid worms	℥ij	gr. 120		
	25 20	"	"	"	Empty	gr. xx	gr. 220		
	26 15	"	2 hrs.	"	"	.....	.....	℥iij	gr. 60
V.	27 15	"	"	"	"	.....	.....	℥iij–gr.xl	gr. 20
	28 10	"	"	Boudault's gr. xv	"	℥j–gr. xx	gr. 160		
	29 9	"	"	"	"	gr. xv	gr. 225		
VI.	30 15	"	2½ hrs.	Also gr. ½ morph. sul.	"	gr. xlv	gr. 195		
	31 9	"	"	"	"	.....	.....	℥ij	gr. 120
	32 9	"	"	"	"	.....	.....	℥ij	gr. 120
	33 8	"	"	"	"	Only traces	gr. 240		
	34 8	"	"	"	Mass of foreign matter.	℥l–gr. xiij	gr. 167		
	35 12	"	"	No morphine	Empty	.....	.....	℥ij–gr.xvj	gr. 102
	36 15	"	1⅔ hrs.	Keasby & Mattison's gr. x	"	gr. xl	gr. 200		

In conclusion: A physician in giving a dose of *good* pepsin may believe that it will have a value two or three times greater than that exhibited under ordinary artificial conditions, *i. e.*, it will digest twenty or thirty times its own weight. This conclusion is in harmony with much clinical experience, that *good* pepsin has a *real* though not a *great* medicinal value.

Points of practical importance are, that large doses should be given, even of so-called pure pepsins. The physician should always know how much pure pepsin there is in the saccharated preparations. Acid should generally be given immediately before, and the pepsin after meals.